THE ANTIPROLIFERATIVE EFFECT OF THE ANTI-ARRHYTHMIC AMIODARONE ON *TRYPANOSOMA CRUZI* AND *LEISHMANIA MEXICANA* IS DRIVEN BY DISRUPTION OF THE MITOCHONDRIAL CALCIUM REGULATION WITHOUT AFFECTING THE HOST CELL.

Gustavo BENAIM

Instituto de Estudios Avanzados (IDEA) & Instituto de Biología Experimental.
Facultad de Ciencias. Universidad Central de Venezuela.
Caracas. Venezuela. E mail:gbenaim@reacciun.ve

Trypanosoma cruzi and *Leishmania mexicana* are the causative agents of Chagas' disease and Leishmaniasis, respectively. These parasites have an essential requirement for ergosterol instead of cholesterol, and it has been shown that newly developed ergosterol biosynthesis inhibitors, such as the anti-fungal posaconazole, have potent trypanocidal activity *in vitro* as well as *in vivo*. We show here that the anti-arrhythmic compound amiodarone, frequently prescribed for the symptomatic treatment of Chagas' disease patients also has direct activity against *T. cruzi*, both *in vitro* and *in vivo,* and that it acts synergistically with posaconazole. Amiodarone disrupts the parasite's Ca^{2+} homeostasis by inducing a rapid release of this cation from the single giant mitochondrion present in those cells, as confirmed by the use of calcium indicators Fura-2 and Rhod-2 and using Rhodamine 123 as indicator of the mitochondrial membrane potential in *T. cruzi infected* cells under confocal microscopy. In addition, amiodarone inhibits *de novo* sterol biosynthesis at the level of oxidosqualene cyclase, therefore strongly potentiating the effects of posaconazole. These results provide logical explanations for the synergistic activity of amiodarone with azoles against *T. cruzi.* Interestingly, similar results were obtained when amiodarone was studied on *Leishmania mexicana*, either in culture or on infected macrophages.
Key words: Calcium, *Trypanosoma cruzi*, *Leishmania mexicana*,